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EPA-registered repellents for mosquitoes transmitting emerging viral disease

Radha V. Patel,^{1,3} Kristy M. Shaeer,^{1,3} Pooja Patel,^{1,2} Aleksey Garmaza,¹ Kornwalee Wiangkham,¹ Rachel B. Franks,^{1,3} Olivia Pane,^{1,2} Nicholas W. Carris,^{1,2}

¹University of South Florida College of Pharmacy; Department of Pharmacotherapeutics and Clinical Research

²University of South Florida Morsani College of Medicine; Department of Family Medicine

³University of South Florida Morsani College of Medicine: Department of Internal Medicine

Correspondence:

Kristy M. Shaeer

Assistant Professor

Colleges of Pharmacy and Medicine

Department of Pharmacotherapeutics & Clinical Research

Department of Internal Medicine

University of South Florida

12901 Bruce B. Downs Blvd., MDC 30 Tampa, FL 33612

Phone: 813.974.0967

Fax: 813.905.9890

Email: kshaeer@health.usf.edu

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Running head: EPA-registered mosquito repellents

Abstract

In many parts of the United States, mosquitoes were previously nuisance pests. However, they now represent a potential threat in the spread of viral diseases. The *Aedes aegypti*, *Aedes albopictus*, and *Culex* species mosquitoes are endemic to the United States and together may transmit a variety of viral diseases of growing concern including West Nile Virus, chikungunya, dengue fever, and Zika virus. The

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Centers for Disease Control and Prevention (CDC) and the Environmental Protection Agency (EPA) recommend N,N-diethyl-meta-toluamide (DEET) as a first-line mosquito repellent, but for patients refusing DEET or other conventional repellents, guidance is limited to any EPA-registered product. Therefore, we conducted a systematic review of the literature to identify which EPA-registered personal mosquito repellent provides the best protection from *A. aegypti*, *A. albopictus* and *Culex* spp. mosquitoes. We abstracted data from 62 published reports of EPA-registered mosquito repellents. The conventional repellent picaridin has the strongest data to support its use as a second-line agent, while IR3535 and oil of lemon eucalyptus are reasonably effective natural products. Citronella, catnip, and 2-undecanone offer limited protection or have limited data. These results can be used by pharmacists and other healthcare professionals to advise patients on the selection of an EPA-registered mosquito repellent. Regardless of the repellent chosen, it is vital for patients to follow all instructions/precautions in the product labeling to ensure safe and effective use.

Introduction

Globalization is expanding international travel and trade, while also facilitating the spread of mosquito-borne illnesses into the United States from other parts of the world where they are endemic.^{1,2} Climate change has contributed to growing mosquito populations and may increase the risk for local transmission.³ *Aedes aegypti*, *Aedes albopictus*, and *Culex* spp. mosquitoes are commonly found in the United States and are capable of transmitting viral diseases such as West Nile Virus, chikungunya, dengue fever, and Zika virus.^{4,5}

West Nile Virus is the most common mosquito-borne illness in the US with 2,205 cases and 97 deaths reported in 43 different states in 2014.⁶ Dengue fever, though not reported as frequently in the U.S. mainland, is endemic to U.S. territories such as Puerto Rico, the U.S. Virgin Islands, Samoa, and Guam.⁷ Prior to 2013, chikungunya cases reported in the United States were travel-related. As of 2014, local transmission of chikungunya has been reported in Florida, Puerto Rico, and the U.S. Virgin Islands.⁸ More recently, Zika virus has rapidly spread worldwide and has caused numerous significant fetal abnormalities and miscarriages.^{9,10} As of August 10, 2016, the Centers for Disease Control and Prevention (CDC) reported 1,962 Zika virus cases reported in the United States have been travel-related,

laboratory-acquired, or transmitted through sexual contact. More recently six locally acquired mosquito-borne cases have been confirmed by the CDC.⁹ Insect repellents are recognized by the Environmental Protection Agency (EPA) and the CDC as a strategy to prevent the local transmission of mosquito-borne illnesses within the United States.¹¹

The EPA and CDC recommend products containing EPA-registered active ingredients for personal use on skin and/or clothing which include: N,N-diethyl-meta-toluamide (DEET), picaridin (also known as: KBR 3023, Bayrepel, and icaridin), IR3535, oil of lemon eucalyptus, para-menthane-3,8-diol (the active ingredient in oil of lemon eucalyptus), catnip oil, 2-undecanone, citronella, and permethrin (applied on clothing only).¹¹⁻¹³ However, DEET is considered the gold-standard ingredient and has an extensive safety track record, including use by children and pregnant patients when applied appropriately (Table 1).^{11,13-17}

Despite assurance from the CDC and EPA regarding the safety of DEET, patients frequently express concern related to conventional repellents (Table 2) and may prefer natural alternatives.^{13,15} Reasons may include concerns of encephalopathy and neurotoxic effects, particularly in children, and may lead patients to use more natural ingredients, which could be viewed as safer, eco-friendly, and just as effective as conventional repellents.^{18,19} Oil of lemon eucalyptus and IR3535 are biopesticides, defined as products derived from or synthetic versions of natural materials (Table 2).^{12,20} Pharmacists, particularly in the community setting, must be knowledgeable about the different types of repellents available, be able to assist in appropriate product selection, and counsel patients on the proper use of these products. However, specific guidance from the CDC regarding insect repellents other than DEET are limited.²⁰ Therefore, the objective of our review was to identify which EPA-registered mosquito repellents provide the best protection against target mosquitoes in order to aid pharmacists and other healthcare professionals in recommending mosquito repellent products in a patient-centered manner.

Methods

Search Strategy and Selection Criteria

We searched Medline through PubMed (up to May 26, 2016) for publications in any language related to the efficacy/effectiveness of mosquito repellents. We included reports that 1) reported original data, 2) were prospective and controlled (active or placebo/untreated), 3) were completed in humans, 4) reported biting or landing outcome, 5) studied DEET, picaridin, IR3535, oil of lemon eucalyptus, para-menthane-3,8-diol, catnip oil, 2-undecanone, citronella, or permethrin for personal use, 6) studied repellent products or active ingredients available in the United States, and 7) reported outcomes against at least one of the following mosquitoes *A. aegypti*, *A. albopictus*, and *Culex* spp. The primary search term used was “mosquito repellent”. Results of the search were assessed by the authors. References of reports for which the full text was retrieved were also reviewed as additional literature sources. Finally, the authors critically reviewed and searched the medical literature for additional pertinent reports using additional search terms (Appendix 1). All studies for which the full text was retrieved were reviewed by two authors for inclusion. Discrepancies in the determination to include a study were decided by consensus of all authors. Figure 1 provides a summary of the search and study inclusion/exclusion.

Data Abstraction and Analysis

Data were initially abstracted by authors using a standardized table (Appendix 2, Table 1, and Table 2). In the case of articles published in a foreign language, an author who was a native speaker/reader served as a translator. Articles for which no author was a native speaker/reader were reviewed by another contributor (see acknowledgements). For one article in French, a collegiate-trained reader/speaker provided a complete translation. Data were reviewed during author meetings. The data abstracted from each study was confirmed by a second author. The following information was retrieved: author; location; number of subjects studied; products/compounds studied; method of product use; study design/type; mosquitoes studied; protection outcome; and study interpretation and potential for bias. For

the analysis, oil of lemon eucalyptus and its active ingredient, para-menthane-3,8-diol, were considered together.

Results

Literature Review

The final database search was performed on May 26, 2016. No date limit was set. A total of 874 citations were returned. Flow of included and excluded reports is described in Figure 1. Following completion of all search strategies a total of 62 reports were included in the final review (Appendix 2, Table 1, and Table 2). Included reports were published between 1970 and 2016 with studies performed in 18 different countries. The breakdown of studies included 36 reports of data from laboratory studies only, 22 reports from field studies only, and 4 reports from both laboratory and field studies. Results were abstracted into Appendix 2, Table 2. Sample size was generally small. The most common controls were varying concentrations of DEET and placebo/untreated. The protection provided by products varied widely between studies. Major contributing factors to this variation included the study design, specific product, density of mosquitoes, mosquito species, and environment. In general, *A. aegypti* was the most aggressive biter and *Culex* spp. were the least aggressive.

Conventional Repellents

DEET in varying formulations and concentrations (4-80%) demonstrated a strong and consistent ability to reduce mosquito biting relative to other repellents, despite variability in mosquito species, mosquito density, and environment (Table 2).²¹⁻³⁵ However, DEET formulations with a concentration greater than or equal to 20% provided longer protection up to 12 hours, compared to lower concentrations of DEET, with protection times between 1 and 6 hours.²¹⁻³⁵ Five studies showed that picaridin at similar concentrations (10-20%) provided comparable protection to DEET for up to 5 hours against *A. aegypti*, *A. albopictus*, and *Culex* spp.³⁶⁻⁴⁰ Four studies of permethrin treated clothing provided favorable protection

time (4-6 weeks) compared to placebo/untreated or DEET alone.⁴¹⁻⁴⁴ Concomitant use of permethrin treated clothing and DEET appears to prolong protection.^{41,43,44} One report demonstrated that DEET wristband repellents provided limited protection (< 1 minute).²²

Biopesticide Repellents (natural products)

Results from four studies suggest similar protection between DEET and IR3535 when used at equal concentrations ranging from 10-20% (Table 2).^{21,32,45,46} Three of these studies tested these products against *Culex* spp. and one against *A. aegypti*.^{21,32,45,46} Results suggests IR3535 20% provides similar protection time (2 hours) as DEET 10% against *A. aegypti*.³² In addition, a head-to-head comparison of IR3535 15-20% and picaridin 10-20%, in both the spray and lotion formulation, resulted in protection of up to 6 hours against *A. aegypti*.⁴⁷ Protection time in three studies comparing oil of lemon eucalyptus and DEET varied anywhere between 2-9 hours.^{37,45,48} One report included *A. aegypti* mosquitoes and used DEET 30%, which demonstrated better reductions in biting than with oil of lemon eucalyptus 10-20%.⁴⁸ The remaining two studies, which showed similar results between DEET and oil of lemon eucalyptus, included only *Culex* spp. mosquitoes, which are less aggressive biters compared to *A. aegypti*.^{37,45} However, four reports of oil of lemon eucalyptus (concentrations up to 50%) demonstrated minimal protection against *A. aegypti* compared to DEET (concentrations as low as 5%).^{33,39,49,50} Citronella at varying concentrations (0.25% - 50%) provided minimal, short duration, or no protection compared to other EPA-registered products.^{22,23,26,32,33,39,51-54} One study found citronella 50% provided protection against *Culex* spp. compared to the untreated control.⁵⁴ Similar to DEET wristbands, citronella wristbands and oil of lemon eucalyptus patches provided minimal to no protection.^{22,52} Only two studies in our review included catnip, which limits the ability to determine its effect. Based on the limited data, catnip does not appear to be as effective as DEET.^{34,55} Similarly, there were limited studies testing 2-undecanone, therefore precluding conclusion.^{56,57}

Discussion

Considering the number and consistency of reports showing that DEET provides superior or equivalent protection, we concluded that DEET – particularly at concentrations greater than or equal to 20% – should remain the repellent of choice to protect against *A. aegypti*, *A. albopictus*, and *Culex* spp.^{21-35,58} The CDC notes that the use of DEET of least 20%, provides longer protection against mosquitoes and protection against ticks and other bugs; concentrations as high as 50% provide even longer protection.⁵⁹ However, protection time also varies with mosquito species, mosquito density, and environment. Therefore, it would be appropriate to recommend a higher concentration DEET-containing repellent when high density or prolonged exposure to mosquitos is expected. Regardless of the DEET concentration used, product specific instructions should be followed for safe use, particularly as it relates to children and pregnancy.

The safety of DEET has previously undergone extensive review.^{15,19} Major adverse events with DEET primarily arise from inappropriate use (Table 1). Because there are no significant safety issues with DEET, and because of the consistent evidence of its ability to protect against mosquitos, we are in agreement with the CDC and EPA on recommending DEET-containing products for children and pregnant/lactating women.^{13,15} It remains important to follow product instructions, which may limit reapplication, particularly in younger children. Therefore, it would be prudent to track the time since application, avoid being in areas with mosquitoes for extended periods of time if possible, and weigh the risks and benefits of the potential for repellent toxicity versus mosquito-borne infection.¹⁶ One strategy for patients to protect themselves with DEET while limiting exposure is to apply DEET to clothing rather than directly to skin.²⁰

While we strongly recommend DEET-containing products as the first-line repellent, we appreciate that patients may have unresolved concerns regarding the safety of DEET despite guidance from the EPA and CDC. While we further recommend counseling patients in an attempt to assuage concerns over DEET, other EPA-registered products are effective and preferred over no treatment. Our review found some evidence of comparable protection between DEET, picaridin, and IR3535 against *Culex* spp. when used at similar concentrations ranging from 10-20%.^{21,36,38,45,46} However, in order for IR3535 and picaridin to protect against *A. aegypti* and *A. albopictus*, a concentration of at least 20% may be necessary to

provide protection similar to DEET-containing product of less than 20%.^{32,39,40} Concentrations of oil of lemon eucalyptus up to 50%, may protect against *Culex* spp. but may require frequent reapplication in order to provide some protection against *A. aegypti* and *A. albopictus*.^{33,37,39,49,50} Overall, we found that picaridin has the most robust data to support it as an alternative to DEET, followed by IR3535 and then oil of lemon eucalyptus. There were no convincing differences in protection between IR3535 and oil of lemon eucalyptus, so we recommend EPA-registered products containing either repellent for patients declining the use of the conventional repellents DEET or picaridin.

Though citronella, catnip, and 2-undecanone are included in the EPA-registered ingredient list, our review of the literature does not support their use.^{22,23,26,32-34,39, 51-57} We identified two reports regarding 2-undecanone, and therefore we recommend against its use over other EPA-registered products with greater supporting data.^{56,57} The data regarding catnip is limited, and suggests that catnip is inferior to other EPA-registered ingredients.^{34,55} Conversely, citronella has a large amount of reported data, but the data consistently demonstrate that citronella offers limited protection time.^{22,23,26,32, 33,39,51-54} Furthermore, the data are poor and limited to support the use of DEET or citronella wristband repellents or the oil of lemon eucalyptus patch.^{22,52}

DEET combined with permethrin-treated clothing may provide additional protection than either alone.^{41,43,44} The use of permethrin treated clothing may be beneficial for individuals engaging in activities with high exposure to mosquitoes for prolonged periods of time, such as hiking or camping. Though permethrin-treated clothing can dramatically decrease mosquito biting, a clear time period of complete protection was not defined. Furthermore, protection wanes with the number of wash cycles. Therefore, patients using permethrin-treated clothing must track the number of wash cycles the clothing has undergone per the specific product's recommendations for use.

To our knowledge, this is the largest review of EPA-registered mosquito repellents for use against *A. aegypti*, *A. albopictus*, and *Culex* spp., which are responsible for transmitting West Nile virus, chikungunya, dengue fever, and Zika virus. Our report offers important clarifying information regarding selection of EPA-registered repellents in patients refusing DEET. The size of our review is an advantage, as generally, individual studies were small. A major strength of our review is inclusion of multiple reports from non-English journals as mosquitoes represent a global problem. Despite the strengths of our report,

it must be taken in context. Regardless of the scope, reviews are limited by design, as we did not perform a meta-analysis. Furthermore, the effect of repellents on mosquitoes may vary with mosquito species, mosquito density, and environment. Inclusion of all global studies presents a limitation; however limiting the review to studies in the United States in the last 10 years would have yielded only three results. Regardless, the results must be considered carefully and in the context of existing guidance.

Our strategy allowed for the greatest possible inclusion of relevant reports. The findings of our report cannot be extrapolated to devices or products intended to repel mosquitoes from an area (e.g. citronella candles), as this was outside the scope of the review. Additionally, the review did not address non-EPA-registered ingredients. While potentially effective, we deemed a priori that we would not recommend such ingredients regardless of the findings as we would not recommend deviation from guidance set forth by the EPA or CDC. Additionally, several studies included in the review did not report specific dosage forms, therefore precluding formulation-specific recommendations. Finally, our findings cannot be extrapolated to other types of mosquitoes as there is a potential for the effect of the repellent to vary by mosquito. Because of this, our review applies to areas endemic to the *A. aegypti*, *A. albopictus*, and *Culex* spp. However, these mosquitoes affect large portions of the United States and are responsible for transmitting viral disease.⁴

Conclusion

It is imperative that healthcare practitioners, particularly those in the community and primary care settings, remain vigilant in recommending that patients avoid unnecessary exposure to mosquitoes. We strongly encourage practitioners to follow recommendations from EPA and CDC while incorporating primary literature and shared decision making into selecting the best mosquito repellent for a given patient. Regardless of the agent selected, it is important for patients to follow all labeling and precautions to avoid potential toxicity from overuse or increased mosquito bite risk from underuse. DEET remains the first choice mosquito repellent and is suitable for use in children and pregnant/lactating women. In patients unwilling to use DEET, preference should be given to products containing picaridin or IR3535, preferably at concentrations at or above 20% in order to provide protection against *A. aegypti* and *A. albopictus*. Oil of lemon eucalyptus, at concentrations greater than 20%, may also be reasonably used

though it may provide less protection. We recommend that patients willing to use only natural products use IR3535 or oil of lemon eucalyptus-containing products. We discourage recommending products with the primary repellent being citronella, catnip, or 2-undecanone as well as formulations of wristbands or patches over other EPA-registered products due to an apparent lack of protection or significant limitations in data. Permethrin-treated clothing may be beneficial in patients seeking to avoid topical repellents altogether. Permethrin may also be particularly useful when combined with DEET or for patients anticipating prolonged exposure to mosquitoes, though complete protection over a defined time period is unlikely if permethrin treated clothing is used alone.

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Table 1 Footnote

1 Table adapted from information presented by the United States Environmental Protection Agency, a governmental agency.

Table 1. Guide for the safe and effective use of repellents.^{1,13,17}

Applying the Product	Other Safety Tips and Tips to Prevent Mosquito Bites
Read and follow the label directions to ensure proper use; be sure you understand how much to apply.	Check the label to see if there are warnings about flammability. If so, do not use around open flames or lit cigarettes.
Apply repellents only to exposed skin and/or clothing. Do not use under clothing.	After returning indoors, wash treated skin and clothes with soap and water.
Do not apply near eyes and mouth, and apply sparingly around ears.	Do not use any product on pets or other animals unless the label clearly states it is for animals.
When using sprays, do not spray directly into face; spray on hands first and then apply to face.	Most insect repellents do not work against lice or fleas.
Never use repellents over cuts, wounds, or irritated skin.	Store insect repellents safely out of the reach of children, in a locked utility cabinet or garden shed.
Do not spray in enclosed areas.	Keep mosquitoes away from exposed skin by wearing long-sleeved shirts, long pants, and socks.
Avoid breathing a spray product.	Tuck shirts into pants and pants into socks to cover gaps in your clothing where mosquitoes can get to your skin.
Do not use it near food.	Stay indoors at sunrise, sunset, and early in the evening when mosquitoes are most active.

Table 2 Footnote

CR = control release; crm = cream; d = day; DEET = N,N-diethyl-meta-toluamide; DMP = dimethyl phthalate; h = hour; IR3535 = Ethyl butylacetylaminopropionate; lft = left; liq = liquid; m = meter; min = minute; N = number of subjects; no. = number; OLE = Oil of Lemon Eucalyptus; PMD = para-menthane-3,8-diol; rt = right; SA = sustained action; sec = seconds; SPF = sun protection factor; wks = weeks

Table 2. Summary of Available Data for Commonly Used Repellents

	Summary of results	Recommendations
Conventional Repellents		
DEET ^{22-40,43-46,48-51,53,55-57}	<ul style="list-style-type: none"> Formulations: solution, soap, crm, impregnated clothing, wristbands, anklets, and cloth fabrics, lotion, stick, liq, aerosol, spray, gel, atomizer Concentrations of 4.75-95% studied Topical application performed better than wristbands which provided Longest protection time (e.g. up to 12 h) against <i>Aedes</i> and <i>Culex</i> spp. 	<ul style="list-style-type: none"> Consistently outperformed biopesticides No benefit observed at concentrations above 50% concentration Adverse effects associated with higher concentration (e.g. skin reactions)
Picaridin ^{36-40,47,51,55}	<ul style="list-style-type: none"> Formulations: solution, liq, lotion, crm, spray Concentrations of 5-20% studied Greater protection time with higher concentrations (e.g. 20%) against <i>Aedes</i> and <i>Culex</i> spp. 	<ul style="list-style-type: none"> Similar repellency as DEET when used at similar concentrations
Permethrin ⁴¹⁻⁴⁴	<ul style="list-style-type: none"> Formulations: impregnated clothing, soap 4-6 weeks protection time with impregnated clothing Soap offered poor and incomplete protection Duration contingent on number of wash cycles Increased protection time with concomitant DEET 	<ul style="list-style-type: none"> Studied only as impregnated clothing or in combination with DEET Beneficial for individuals involved in prolonged activities outdoors with risk of high mosquito exposure Option if individual prefers to completely avoid topical application
Biopesticide/Natural Repellents		
IR3535 ^{21,22,32,33,46,47,51}	<ul style="list-style-type: none"> Formulations: solution, crm, spray, gel, roll on, lotion Concentrations of 1-20% studied Greater protection than citronella Protection of 20% concentration similar to DEET though evidence less consistent 	<ul style="list-style-type: none"> Provided most consistent protection among biopesticide agents Use formulations with a concentration of at least 20% if possible
OLE / PMD ^{23,33,37,39,45,48-52,55}	<ul style="list-style-type: none"> OLE formulations: solution, lotion, oil, spray, patch Topical application performed better than wristbands and patch which provided little or no protection Concentrations of 0.25-50% studied Higher concentrations ($\geq 20\%$) offer better protection time Afforded up to 5 h of protection Protection greater versus <i>Culex</i> spp than <i>Aedes</i> spp Better protection than citronella 	<ul style="list-style-type: none"> Less protection vs. DEET and IR3535 Higher concentration product applied topically preferred for offering best protection
Citronella ^{22,23,26,32,33,39,51-55}	<ul style="list-style-type: none"> Formulations: oil, wristband, spray, lotion Concentrations of 14-50% studied Limited protection time Topical application performed better than wristbands which provided little or no protection 	<ul style="list-style-type: none"> Consistently provided less protection compared to other agents
Catnip ^{34,55}	<ul style="list-style-type: none"> Inconsistent results 	<ul style="list-style-type: none"> Unable to generalize due to

	<ul style="list-style-type: none"> Limited data demonstrates DEET more effective Formulation: oil 	limited number of studies
2-undecanone ^{56,57}	<ul style="list-style-type: none"> Inconsistent results Formulation: spray, cloth patch 	<ul style="list-style-type: none"> Unable to generalize due to limited number of studies

Figure 1 Legend

Flow diagram of study selection.

